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Comparative effectiveness of high dose versus adjuvanted influenza vaccine: A retrospective cohort study

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ABSTRACT

Background: Adults 65 years and older (seniors) experience more complications following influenza infection than younger adults. We estimated the relative vaccine effectiveness (rVE) of a trivalent high dose (HD-IIV3) versus an adjuvanted trivalent influenza vaccine (aIIV3) in seniors for respiratory-related hospitalizations.

Methods: We conducted a retrospective cohort study using claims data from Optum's Clinformatics® Data Mart to compare outcome rates between seniors who received HD-IIV3 versus aIIV3 during the 2016/17 and 2017/18, predominantly A/H3N2 respiratory seasons. Rates were adjusted for demographic characteristics, comorbid conditions, previous influenza vaccination, and geography. We used the previous event rate ratio (PERR) approach to address bias by time-fixed unmeasured confounders.

Results: We identified 842,282 HD-IIV3 and 34,157 aIIV3 recipients for the 2016/17 season and 1,058,638 HD-IIV3 and 189,636 aIIV3 recipients for the 2017/18 season. The pooled rVE of HD-IIV3 versus aIIV3 for respiratory-related hospitalizations over both seasons was 12% (95% confidence interval: 3.3%–20%); 13% (−6.4% to 32%) for the 2016/17 season and 12% (2.1%–21%) for the 2017/18 season.

Conclusions: Pooled over two predominantly A/H3N2 respiratory seasons, HD-IIV3 was associated with fewer respiratory hospital admissions than aIIV3 in senior members of large national managed health care company in the U.S.

1. Background

Adults 65 years and older (hereinafter referred to as seniors) are at greater risk for complications following influenza infection compared with younger adults, due in part to immunosenescence and increased comorbid conditions, leading to decreased vaccine efficacy and increased severity of influenza-related complications [1,2]. As a result, influenza-associated hospitalization and mortality rates are significantly higher in this age group [3–6]. In the 2017–18 respiratory season, seniors in the United States (U.S.) were estimated to have incurred over 650,000 influenza-associated hospitalizations and 65,000 influenza-associated deaths – 69% and 86% of the total number of influenza-associated hospitalizations and deaths, respectively [7]. Vaccination is the best preventive strategy against influenza infection [8]. As the U.S. population continues to age, it has become vitally important to use influenza vaccines that have demonstrated improved health outcomes in this high-risk population.

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Standard dose (SD) inactivated influenza vaccines are derived from egg-grown viruses and contain 15 μg of hemagglutinin (HA) from each of three (trivalent, SD-IIV3, 45 μg HA total) or four (quadrivalent, SD-IIV4, 60 μg HA total) strains and are licensed in the U.S. for use in individuals 6 months of age or older. Due to immunosenescence, there is a need for vaccines that provide better protection than SD among seniors. Currently in the U.S., two influenza vaccines are licensed exclusively for use in seniors: an egg-grown trivalent inactivated high dose (HD-IIV3) influenza vaccine (Fluzone® High-Dose, Sanofi Pasteur) and an egg-grown trivalent inactivated adjuvanted (aIIV3) influenza vaccine (Fluad®, Seqirus). HD-IIV3 aims to improve protection through quadrupling the dose per influenza strain from 15 μg HA to 60 μg HA (180 μg total) whereas aIIV3 is an SD-IIV3 vaccine to which an oil-in-water emulsion of squalene oil (MF59) is added.

In a randomized clinical trial (RCT), HD-IIV3 demonstrated superior efficacy (pre-specified superiority criterion: lower limit of the 2-sided 95% confidence interval (CI): >9.1%) in preventing clinically-relevant influenza disease, compared to SD-IIV3 [9]. In a *meta*-analysis of 7 studies that were conducted after licensure, HD-IIV3 was associated with less influenza-like illness compared to SD-IIV3 (rVE of 19.5%; 95% CI: 8.6–29.0%), with less hospitalized pneumonia (rVE of 24.3%, 95% CI: 13.9–33.4%) and with less hospitalizations for cardiorespiratory disease (rVE of 18.2%; 95% CI: 6.8–28.1%) [10]. Individual studies conducted among various populations during the 2011–12 through 2017–18 seasons have reported HD-IIV3 to be associated with reduced influenza-related complications compared to SD-IIV3 [11–18].

Although a few observational studies report that aIIV3 was associated with reduced influenza-related complications in seniors as compared to SD-IIV3 [18–20], no RCTs have evaluated the relative efficacy of aIIV3 against laboratory-confirmed influenza in seniors [21]. A meta-analysis, which included 39 trials comparing adults 60 years of age or older, who received either intradermal IIV3, HD-IIV3, or aIIV3, reported that both HD-IIV3 and aIIV3 demonstrated a significantly higher post-vaccination geometric mean titer to A(H3N2), as compared to SD-IIV3. Specifically, HD-IIV3 induced 82% higher titers to A(H3N2) as compared to SD-IIV3, which was statistically significantly higher than the 52% higher titers induced by aIIV3. In addition, HD-IIV3 elicited higher antibody titers in response to A(H1N1) and B/Victoria viruses, as compared to SD-IIV3 [22].

The recent utilization of both HD-IIV3 and aIIV3 in the U.S. enables the use of routinely collected data to assess the comparative effectiveness of the two vaccines. Recently, the first such observational study (Izurieta et al., J Infect Dis, 2018) reported that HD-IIV3 was associated with fewer influenza-related hospital encounters than aIIV3 (rVE of 7.7%, 95% CI: 5.1%, 10.2%) [18]. This study relied on exposure modeling methods (propensity score) that only adjust for measured confounding variables, but cannot account for unmeasured ones [23]. Frailty, for instance, is a confounder that may influence choice of vaccine, but may be hard to capture using claims data [15]. As such, there is a need for further comparative effectiveness research using methods that, to some extent, can address confounding by unmeasured variables. Here, we use the previous event rate ratio (PERR) approach, which adjusts for measured and unmeasured time-fixed confounders, to provide further evidence on the comparative effectiveness of HD-IIV3 versus aIIV3.

2. Methods

2.1. Design and data sources

We conducted a retrospective cohort study using claims data from Optum's Clinformatics® Data Mart (CDM) to compare outcome rates between recipients of HD-IIV3 and aIIV3 during two respiratory seasons: 2016/17 and 2017/18.

CDM is derived from a database of administrative health claims for members of a large national managed care company affiliated with Optum (hereinafter referred to as members). The database includes approximately 17–19 million annually covered members, for a total of over 60 million unique members over a 9 year period (1/2007 through 12/2018). CDM is statistically de-identified under the Expert Determination method consistent with HIPAA [24,25]. The administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion. CDM data comprises both commercial and Medicare Advantage health plan data. The population is geographically diverse, spanning all 50 states. In addition to medical claims and pharmacy claims, the data includes information on member eligibility and inpatient confinements.

2.2. Study population and influenza vaccination

The study population included all members aged 65 years and older at time of vaccination. Vaccinations received in a doctor's office were identified by Current Procedural Terminology (CPT) codes (HD-IIV3 vaccine CPT code: 90662, aIIV3 vaccine CPT code: 90653) or National Drug Code (NDC, Supplemental Table 2). Vaccinations received in a community pharmacy were identified by brand names.

2.3. Study periods

Following prior work [26], we defined the start of the respiratory season as July 1 and the end as June 30 of the next calendar year. Within each respiratory season, we defined a baseline period starting on July 1 and ending on the day of vaccination. We used this period as an indicator for confounding, because here the vaccines will have no impact on the outcome rates: a treatment effect in this period could be an indicator for residual confounding [27]. Allowing for immunological response following vaccination, the observation period started two weeks after vaccination and ended at the end of the respiratory season on June 30. Here, outcome rates may be influenced by the vaccines. Baseline characteristics were observed during one year before vaccination.

2.4. Inclusion and exclusion criteria

To increase the probability of capturing a member's baseline characteristics and outcomes, we included members with continuous enrollment starting at least one year before vaccination and ending not before the end of the respiratory season on June 30. If a member dies during this period, we counted their enrollment until the month of death. We applied two exclusion criteria. First, members for whom we found more than one vaccination record per respiratory season were excluded. Second, members with an observation period less than two weeks – due to late vaccination or death – were excluded. We relaxed these inclusion and exclusion criteria in a stability analysis [28].

2.5. Baseline characteristics

We classified members on demographic characteristics; month, region and point of vaccination (community pharmacy versus doctor's office); influenza vaccination in the previous season; and by presence of certain health conditions (Table 1). We captured baseline characteristics during a period of one year before vaccination. We identified the 17 medical conditions used to calculate the Deyo-Charlson score by primary and secondary discharge diagnosis codes (International Classification of Diseases [ICD]-10) from

outpatient visits and hospital admissions. We deemed a condition present on the basis of a qualifying ICD code from a single hospital admission or two outpatient visits.

2.6. Outcomes

The primary outcome of the study was any hospitalization in which the patient record indicated a respiratory condition (ICD-10-CM: Jxx) as the principal discharge diagnosis [29]. The secondary outcome was any hospitalization for a cardio-respiratory condition (ICD-10-CM: Ixx – Jxx). We report hospitalizations for a urinary tract infection (UTI) as a test-negative control outcome because we do not expect these to be preventable by either influenza vaccine. Additionally, we explored stratification of primary and secondary outcomes by more specific disease groups (e.g. hospitalizations for pneumonia, Supplemental Tables 1, 5 and 6).

2.7. Statistical analysis

We are interested in comparing the effectiveness of the HD-IIV3 and aIIV3 vaccines. Because we expected confounding by indication – resulting in treatment selection bias – by variables that are either unmeasured or measured inaccurately (e.g. baseline comorbidities), we employed the previous event rate ratio (PERR) approach, which adjusts for measured and unmeasured, time-fixed confounding factors [30–32]. This approach, a type of difference-in-differences analysis [33], compares the outcome rate change from baseline to observation period in the HD-IIV3 cohort with the rate change in the aIIV3 cohort (Supplemental Fig. 1). These rate changes can be rewritten as the change in the relative risk from baseline (RR_b) to observation period (RR_o), or ($\frac{RR_o}{RR_b}$): a measure of the treatment effect adjusted for unmeasured time-fixed confounding variables (variables that are constant during the baseline and observation periods of a given respiratory season). We selected the PERR method because its performance to reduce bias caused by unmeasured confounding factors has been thoroughly described, both in simulation studies [30,32,34] and an empirical study comparing PERR estimates with RCTs [35]. The crude (unadjusted for measured baseline variables) relative vaccine effectiveness (rVE) is calculated as

$$rVE = \left(1 - \frac{RR_o}{RR_b}\right) \times 100\% \quad (1)$$

We estimated crude rVEs by fitting a Poisson regression model with an interaction term between two variables, the *period* (observation versus baseline) and the*treatment* (HD-IIV3 versus aIIV3). The regression model is shown below.

$$\log(E(Y)) = season + period + treatment +$$

$$season \times period + season \times treatment + period \times treatment +$$

$$season \times period \times treatment + \log(\text{daysatrisk}) \quad (2)$$

The coefficient of the interaction term $period \times treatment$ is used to estimate $\left(\frac{RR_o}{RR_b}\right)$, and thus the crude rVE. We adjusted the crude rVE for measured confounders by adding all baseline characteristics of Table 1 as covariates to the model above (model 2, except for Age Groups and the Deyo-Charlson Score, to prevent collinearity with Age and individual comorbid conditions). Pooled results over the two seasons were also calculated by removing

Table 1
Baseline characteristics of high dose (HD-IIV3) and adjuvanted influenza vaccine (aIIV3) recipients.

	Season 2016/17					Season 2017/18				
	HD-IIV3		aIIV3		SMD*	HD-IIV3		aIIV3		SMD*
Study Population	842,282		34,157			1,058,638		189,636		
Gender										
Male	351,264	42%	14,474	42%	−0.01	443,049	42%	79,031	42%	0.00
Female	490,969	58%	19,683	58%	0.01	615,545	58%	110,596	58%	0.00
Unknown	49					44		9		
Race										
Asian	23,751	2.8%	1,000	2.9%	−0.01	29,845	2.8%	4,801	2.5%	0.02
African American	54,599	6.5%	1,896	5.6%	0.04	75,833	7.2%	15,011	7.9%	−0.03
Hispanic	61,328	7.3%	2,296	6.7%	0.02	76,975	7.3%	11,645	6.1%	0.05
White	569,019	68%	23,351	68%	−0.02	689,639	65%	124,306	66%	−0.01
Unknown Race	138,384	16%	5,728	17%	−0.01	168,024	16%	30,818	16%	−0.01
Age										
65–69	189,369	22%	8,096	24%	−0.03	233,431	22%	42,784	23%	−0.01
70–74	234,809	28%	10,060	29%	−0.03	307,216	29%	57,242	30%	−0.03
75–79	175,214	21%	7,116	21%	0.00	227,916	22%	40,576	21%	0.00
80–84	125,263	15%	4,736	14%	0.03	150,231	14%	25,772	14%	0.02
85+	117,627	14%	4,149	12%	0.05	139,844	13%	23,262	12%	0.03
Age (mean, sd)	75.57	6.67	75.14	6.49	0.07	75.46	6.71	75.22	6.61	0.04
HHS Region										
Region 1: CT, ME, MA, NH, RI, VT	31,004	3.7%	3,437	10%	−0.25	40,951	3.9%	8,004	4.2%	−0.02
Region 2: NJ, NY, PR, VI	62,302	7.4%	2,993	8.8%	−0.05	72,956	6.9%	15,392	8.1%	−0.05
Region 3: DE, DC, MD, PA, VA, WV	27,988	3.3%	619	1.8%	0.10	33,411	3.2%	4,737	2.5%	0.04
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	210,553	25%	7,359	22%	0.08	251,396	24%	79,399	42%	−0.39
Region 5: IL, IN, MI, MN, OH, WI	165,564	20%	6,221	18%	0.04	204,987	19%	26,293	14%	0.15
Region 6: AR, LA, NM, OK, TX	83,243	10%	3,193	9.3%	0.02	118,510	11%	10,684	5.6%	0.20
Region 7: IA, KS, MO, NE	38,421	4.6%	1,177	3.4%	0.06	57,121	5.4%	4,040	2.1%	0.17
Region 8: CO, MT, ND, SD, UT, WY	59,664	7.1%	3,159	9.2%	−0.08	74,882	7.1%	7,596	4.0%	0.13
Region 9: AZ, CA, GU, HI, NV	122,521	15%	3,773	11%	0.10	155,834	15%	22,016	12%	0.09
Region 10, AK, ID, OR, WA	39,264	4.7%	2,151	6.3%	−0.07	46,356	4.4%	11,108	5.9%	−0.07
Unknown Region	1,758	0.2%	75	0.2%	0.00	2,234	0.2%	367	0.2%	0.00

Table 1 (*continued*)

	Season 2016/17					Season 2017/18				
	HD-IIV3		aIIV3		SMD*	HD-IIV3		aIIV3		SMD*
Study Population	842,282		34,157			1,058,638		189,636		
Month of Vaccination										
August & September	298,370	35%	7,009	21%	0.34	354,103	33%	60,234	32%	0.04
October	335,082	40%	9,497	28%	0.26	437,160	41%	77,418	41%	0.01
November	130,471	15%	8,711	26%	−0.25	160,983	15%	28,144	15%	0.01
December & January	68,463	8.1%	7,886	23%	−0.42	91,407	8.6%	20,429	11%	−0.07
Other	9,896	1.2%	1,054	3.1%	−0.13	14,985	1.4%	3,411	1.8%	−0.03
Time at risk										
Baseline period (mean, sd)	107	33	129	41	−0.58	108	35	110	39	−0.05
Observation period (mean, sd)	242	35	221	42	0.56	241	37	239	40	0.04
Point of Vaccination										
Community Pharmacy	413,339	49%	24,277	71%	−0.46	513,661	49%	135,577	71%	−0.48
Doctor's office	440,955	52%	10,444	31%	0.45	564,019	53%	56,924	30%	0.49
Frailty Proxy										
No hospitalization record found	743,299	88%	30,458	89%	−0.03	930,074	88%	168,412	89%	−0.03
All-cause hospitalizations (mean, sd)	0.19	0.64	0.17	0.60	0.03	0.19	0.66	0.17	0.61	0.03
Study Population	842,282		34,157			1,058,638		189,636		
Comorbid Conditions										
No record of comorbid conditions found	401,006	48%	17,782	52%	−0.09	482,522	46%	90,969	48%	−0.05
Myocardial Infarction	23,500	2.8%	864	2.5%	0.02	32,502	3.1%	5,284	2.8%	0.02
Congestive Heart Failure	60,669	7.2%	2,094	6.1%	0.04	84,497	8.0%	13,278	7.0%	0.04
Peripheral Vascular Disease	77,503	9.2%	2,721	8.0%	0.04	107,632	10%	17,441	9.2%	0.03
Cerebrovascular Disease	52,437	6.2%	1,981	5.8%	0.02	69,223	6.5%	11,869	6.3%	0.01
Dementia	25,859	3.1%	1,040	3.0%	0.00	34,905	3.3%	5,638	3.0%	0.02
Chronic Pulmonary Disease	107,899	13%	3,970	12%	0.04	146,273	14%	24,726	13%	0.02
Connective Tissue / Rheumatic Disease	22,506	2.7%	809	2.4%	0.02	29,583	2.8%	5,055	2.7%	0.01
Peptic Ulcer Disease	5,230	0.6%	178	0.5%	0.01	6,778	0.6%	1,207	0.6%	0.00
Mild Liver Disease	14,929	1.8%	581	1.7%	0.01	21,396	2.0%	3,732	2.0%	0.00
Diabetes without complications	193,794	23%	7,046	21%	0.06	258,211	24%	43,469	23%	0.03
Diabetes with complications	81,327	10%	2,786	8.2%	0.05	121,912	12%	19,301	10%	0.04
Paraplegia and Hemiplegia	3,958	0.5%	145	0.4%	0.01	5,738	0.5%	873	0.5%	0.01
Renal Disease	102,056	12%	3,437	10%	0.07	138,137	13%	22,069	12%	0.04
Cancer	76,567	9.1%	2,926	8.6%	0.02	96,641	9.1%	16,965	8.9%	0.01
Moderate or Severe Liver Disease	1,407	0.2%	54	0.2%	0.00	2,015	0.2%	327	0.2%	0.00
Metastatic Carcinoma	6,897	0.8%	248	0.7%	0.01	9,323	0.9%	1,468	0.8%	0.01
AIDS/HIV	579	0.1%	18	0.1%	0.01	891	0.1%	162	0.1%	0.00
Deyo-Charlson Score (mean, sd)	1.38	1.94	1.22	1.82	0.08	1.50	2.06	1.38	1.96	0.06
Vaccinated in previous season										
No vaccination record found	155,647	18%	7,568	22%	−0.09	221,972	21%	40,370	21%	−0.01
HD-IIV3	501,035	59%	17,464	51%	0.17	655,102	62%	105,145	55%	0.13
aIIV3	19	0.0%	4	0.0%	−0.01	17,423	1.6%	12,007	6.3%	−0.24
SD-IIV3	110,739	13%	6,524	19%	−0.16	79,540	7.5%	18,816	9.9%	−0.09
SD-IIV4	73,769	8.8%	2,494	7.3%	0.05	82,138	7.8%	12,217	6.4%	0.05
Other vaccine	1,073	0.1%	103	0.3%	−0.04	2,463	0.2%	1,081	0.6%	−0.05

HD-IIV3: high dose, trivalent; aIIV3: adjuvanted, trivalent; SD-IIV3: standard dose, trivalent; SD-IIV4: standard dose, quadrivalent; Other vaccine: cell culture-based, quadrivalent; recombinant, quadrivalent; live-attenuated, quadrivalent.

* Common characteristics between the HD-IIV3 and aIIV3 cohorts with an absolute standardized mean difference (SMD) of more than or equal to 0.10 suggests a substantial difference between groups.

the interaction term *season* × *period* × *treatment*. We used a robust variance estimator for each rVE, and after exponentiation, the delta-method to calculate 95% confidence intervals.

We compared baseline characteristics between HD-IIV3 and aIIV3 recipients using standardized mean differences. We adopted the rule that an absolute standardized mean difference smaller than 0.1 suggests no substantial difference between the compared groups [36].

2.8. Stability analyses

Supplemental Tables 7–15 catalog the various additional analyses we performed to evaluate the stability of our main results with slightly different study design choices [28]. Given the fact that the PERR method only adjusts for time-fixed unmeasured confounding factors, and the likelihood of potential time (baseline to observation period) dependent unmeasured confounders to be correlated with geographic location, we compared results from our primary analysis with results stratified by state, the smallest geographic area in our data set (Supplemental Tables 7 and 8). In addition, we compared results from the primary analysis with a matched cohort on state and both state and month of vaccination (Supplemental Table 9), both crude and adjusted for baseline characteristics (Supplemental Table 10). In addition to comparing the primary analysis to the matched cohorts, we also ran a primary analysis where we added state level characteristics (Supplemental Table 4) as covariates to the Poisson regression: our attempt to reduce unmeasured confounding factors that are potentially time (period) dependent (Supplemental Table 10, Primary Analysis+). Because of the small number of aIIV3 recipients in 2016–17, we limited all state level adjustments, stratification and matching to the 2017–18 season.

Given the fact that the PERR method uses longitudinal data, we evaluated if patient-level clustering influenced our main analyses by repeating them using generalized estimating equation methods with the independent (Supplemental Table 12) and autoregressive-1 (Supplemental Table 13) working correlation structure. Given the fact that Poisson regression assumes limited heterogeneity of the study population, we evaluated if overdispersion in the outcome data influenced our main analyses by fitting a negative binomial regression (Supplemental Table 14). Because temporal differences between vaccination date and peak of the circulating viral activity

vary by geography, we evaluated if these differences were sufficiently adjusted for in our main analyses by repeating them after matching on vaccination month and region (Supplemental Table 14) [37]. Possible heterogeneity of insurance plans (e.g., different co-pays) can influence a member's choice of one vaccine over the other. We evaluated if heterogeneity of insurance plans influenced our main analyses by adjusting for the 83 most common insurance plans: the most granular stratification with at least one member in each stratum during the two seasons (Supplemental Table 14). In the last stability analysis, we assessed the effects of relaxing the inclusion and exclusion criteria on the main results. Because we required continuous enrollment until the end of the observation period or death, whichever came first, we evaluated if dropping this complete case requirement influenced our main analysis. Instead, we required enrollment only to last until the start of the observation period with a minimum length of the observation period of one day (instead of 14 days). Missing outcome data – lost to follow-up – was addressed weighting complete cases with the inverse of a member's propensity of having a complete case, using the baseline characteristics of Table 1 and insurance plan type of all cases – complete and incomplete. In addition we only counted the first hospitalization. We censored person-time after the first hospitalization, death, or the end of the observation period, whichever occurred first (Supplemental Table 15).

3. Results

We identified 842,282 HD-IIV3 and 34,157 aIIV3 recipients for the 2016/17 season and 1,058,638 HD-IIV3 and 189,636 aIIV3 recipients for the 2017/18 season. Table 1 lists all baseline characteristics. Gender, race, age groups, number of all-cause hospitalizations and comorbid conditions were not substantially different (absolute SMD less than to 0.1) between HD-IIV3 and aIIV3 recipients. We did however observe substantial differences (absolute SMD greater than, or equal to 0.1) in a number of baseline characteristics. Some substantial differences were only observed in one season: these were in geographic region and month of vaccination. In 2016/17, Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Maine) received substantially more aIIV3 vaccinations than HD-IIV3 vaccinations, while in 2017/18 the biggest difference was observed in Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North and South Carolina and Tennessee). In 2016/17, aIIV3 recipients received their vaccine, on average, 3 weeks later than HD-IIV3 recipients, but we didn't observe a difference in 2017/18.

Other baseline characteristics were substantially different in both seasons: the point of vaccination and the vaccination history. We observed that 52% of HD-IIV3 recipients received their vaccine in a doctor's office, compared to 30% of aIIV3 recipients. In 2017/18, 62% of all HD-IIV3 recipients received HD-IIV3 in the previous season compared to 55% of all aIIV3 recipients. 6.3% of all aIIV3 recipients had received aIIV3 in the previous season compared to 1.6% of all HD-IIV3 recipients.

All imbalances in baseline characteristics were addressed by including the variables of Table 1 as covariates in the adjusted regression analysis.

During the baseline period, we observed statistically significant higher hospitalization rates for respiratory disease among members who would eventually receive HD-IIV3 (Table 2). Crude rate ratios (HD-IIV3 versus aIIV3) were 1.29 (95% CI: 1.03, 1.54) and 1.28 (95% CI: 1.16, 1.42) for the 2016/17 and 2017/18 seasons, respectively. During the observation period, however, the difference was less pronounced: 1.09 (95% CI: 0.68, 1.61) and 1.15 (0.93, 1.39) for the 2016/17 and 2017/18 seasons, respectively, resulting in a crude rVE of HD-IIV3 versus aIIV3 of 15% (95% CI: −4.3%, 34%) in 2016/17 and 11% (95% CI: 1.0%, 20%) in 2017/18.

After adjusting the respiratory hospitalization rates for baseline characteristics listed in Table 1, adjusted rate ratios (HD-IIV3 versus aIIV3) during the baseline period were 1.13 (95% CI: 0.91, 1.35) and 1.14 (95% CI: 1.03, 1.25) for the 2016/17 and 2017/18 seasons, respectively (Table 3), suggesting residual bias caused by unmeasured confounding factors. During the observation period the adjusted rates were 0.98 (95% CI: 0.61, 1.44) and 1.01 (0.81, 1.22) for the 2016/17 and 2017/18 seasons, respectively. We estimated an adjusted rVE of HD-IIV3 versus aIIV3 of 13% (95% CI: −6.4%, 32%) in 2016/17 and 12% (95% CI: 2.1%, 21%) in 2017/18 (Supplemental Fig. 1). Pooling the data from both season resulted in an adjusted summary rVE of 12% (3.3, 20%), Table 4.

For our secondary outcome, hospitalizations for cardio-respiratory disease, the crude rVE of HD-IIV3 versus aIIV3 was 14% (95% CI: 4.0%, 25%) in 2016/17 and 5% (95% CI: −0.1%, 10%) in 2017/18. After adjusting these hospitalization rates for baseline characteristics listed in Table 1, the adjusted rVE was 13% (95% CI: 2.3%, 23%) in 2016/17 and 6% (95% CI: 0.6%, 11%) in 2017/18. Pooling the data from both seasons resulted in an adjusted summary rVE of 7% (2.3, 12%). For our test-negative control, hospitalizations for UTI, the adjusted rVE was −20% (95% CI: −95%, 18%) in 2016/17 and 3% (95% CI: −12%, 17%) in 2017/18. Pooling the data from both season resulted in an adjusted summary rVE of −1% (−15, 13%), suggesting no treatment effect.

Table 2
Crude rates, rate ratios (RR) and relative vaccine effectiveness (rVE) with 95% confidence intervals for aIIV3 and HD-IIV3 (HD) recipients in the baseline and observation periods for respiratory seasons 2016–17 and 2017–18.

		Baseline period			Observation period			
Outcome		No	Rate	RR	No	Rate	RR	rVE*
Season 2016-17								
Respiratory disease	aIIV3	121	101 (81, 120)		513	248 (156, 362)		
	HD	3,193	129 (84, 185)	1.29 (1.03, 1.54)	15,169	272 (106, 581)	1.09 (0.68, 1.61)	15% (−4.3%, 34%)
Cardio-respiratory disease	aIIV3	482	400 (359, 441)		1,584	767 (605, 947)		
	HD	12,361	500 (402, 609)	1.25 (1.12, 1.38)	45,738	819 (508, 1255)	1.07 (0.84, 1.32)	14% (4.0%, 25%)
Urinary Tract Infection	aIIV3	70	58 (43, 73)		144	70 (35, 115)		
	HD	1,610	65 (35, 104)	1.12 (0.82, 1.42)	5,042	90 (23, 250)	1.29 (0.65, 2.16)	−16% (−53%, 22%)
Season 2017-18								
Respiratory disease	aIIV3	622	109 (99, 119)		3,293	265 (217, 318)		
	HD	4,390	140 (115, 167)	1.28 (1.16, 1.41)	21,260	304 (201, 443)	1.15 (0.93, 1.39)	11% (1.0%, 20%)
Cardio-respiratory disease	aIIV3	2,572	451 (431, 471)		9,918	797 (723, 876)		
	HD	16,639	531 (483, 581)	1.18 (1.12, 1.23)	62,269	891 (726, 1083)	1.12 (1.00, 1.24)	5% (−0.1%, 10%)
Urinary Tract Infection	aIIV3	332	58 (51, 65)		1,064	86 (65, 109)		
	HD	2,036	65 (50, 82)	1.12 (0.97, 1.26)	6,558	94 (53, 154)	1.10 (0.82, 1.42)	1.8% (−13%, 16%)

Rates are in number of outcomes (No) per 10,000 person-years. Hospitalizations were classified using the principal discharge diagnosis. Confidence intervals were calculated using a robust variance estimator. We applied the Previous Event Rate Ratio (PERR) to address unmeasured confounders by including an interaction term of Period (observation versus baseline period) and treatment (HD-IIV3 versus aIIV3).

Table 3
Rate ratios (RR) and relative vaccine effectiveness (rVE) with 95% confidence intervals for aIIV3 and HD-IIV3 recipients in the baseline and observation periods for respiratory seasons 2016–17 and 2017–18, crude and adjusted for baseline characteristics.

	Baseline period		Observation period			
Hospitalizations	RR, crude	RR, adjusted	RR, crude	RR, adjusted	rVE*, crude	rVE*, adjusted
Season 2016–17						
Respiratory disease	1.29 (1.03, 1.54)	1.13 (0.91, 1.35)	1.09 (0.68, 1.61)	0.98 (0.61, 1.44)	15% (−4.3%, 34%)	13% (−6.4%, 32%)
Cardio-respiratory disease	1.25 (1.12, 1.38)	1.11 (1.00, 1.23)	1.07 (0.84, 1.32)	0.97 (0.77, 1.20)	14% (4.0%, 25%)	13% (2.3%, 23%)
Urinary Tract Infection	1.12 (0.82, 1.42)	0.98 (0.72, 1.24)	1.29 (0.65, 2.16)	1.17 (0.59, 1.96)	−16% (−53%, 22%)	−20% (−59%, 19%)
Season 2017–18						
Respiratory disease	1.28 (1.16, 1.41)	1.14 (1.03, 1.25)	1.15 (0.93, 1.39)	1.01 (0.81, 1.22)	11% (1.0%, 20%)	12% (2.1%, 21%)
Cardio-respiratory disease	1.18 (1.12, 1.23)	1.07 (1.02, 1.12)	1.12 (1.00, 1.24)	1.01 (0.91, 1.11)	5% (−0.1%, 10%)	6% (0.6%, 11%)
Urinary Tract Infection	1.12 (0.97, 1.26)	1.01 (0.88, 1.14)	1.10 (0.82, 1.42)	0.99 (0.73, 1.28)	1.8% (−13%, 16%)	2.5% (−12%, 17%)

Rates are in number of outcomes (No) per 10,000 person-years. Hospitalizations were classified using the principal discharge diagnosis. Confidence intervals were calculated using a robust variance estimator. We applied the Previous Event Rate Ratio (PERR) to address unmeasured confounders by including an interaction term of Period (observation versus baseline period) and treatment (HD-IIV3 versus aIIV3). The Rate rations and PERR were adjusted for observed confounding factors by including all the baseline characteristics of Table 1 as covariates, except for Age Groups and the Deyo-Charlson Score, to prevent collinearity with Age and individual comorbid conditions. Hospitalizations were classified using the principal discharge diagnosis.

Table 4
Relative vaccine effectiveness (rVE) with 95% confidence intervals of high dose (HD-IIV3) versus adjuvanted influenza vaccine (aIIV3) for respiratory seasons 2016–17, 2017–18 and the two seasons combined (summary rVE), adjusted for baseline characteristics.

Hospitalizations	2016–17 season	2017–18 season	Summary rVE
Respiratory disease	13% (−6.3%, 32%)	12% (2.1%, 21%)	12% (3.3%, 20%)
Cardio-respiratory disease	13% (2.3%, 23%)	6% (0.6%, 11%)	7.0% (2.3%, 12%)
Urinary Tract Infection	−20% (−59%, 19%)	2.5% (−12%, 17%)	−0.7% (−14%, 13%)

Confidence intervals were calculated using a robust variance estimator. We applied the Previous Event Rate Ratio (PERR) to address unmeasured confounders by including an interaction term of Period (observation versus baseline period) and treatment (HD-IIV3 versus aIIV3). The PERR was adjusted for observed confounding factors by including all the baseline characteristics of Table 1 as covariates, except for Age Groups and the Deyo-Charlson Score, to prevent collinearity with Age and individual comorbid conditions. Hospitalizations were classified using the principal discharge diagnosis.

3.1. Stability analyses

We observed low numbers of hospitalizations for respiratory disease for the 2017–18 season when stratified by state, limiting the conclusions than can be drawn from these results (Supplemental Tables 7 and 8). Two matched cohort analyses for the 2017–18 season: one on state only, and another on both state and month of vaccination, resulted in higher rVEs compared to the primary analysis of season 2017–18 (Supplemental Tables 9 and 10). The higher rVEs were mainly driven by higher rate ratios in the baseline period, suggesting increased residual confounding. Pooled results from the matched analysis over two seasons on vaccination month and region to adjust for temporal and geographic heterogeneity were similar to the results of the main analysis (Supplemental Table 14). Results of a stability analysis where we added state level characteristics as covariates to the Poisson regression of the primary analysis, as well as all other stability analyses, were similar to the results of the main analysis (Supplemental Tables 11–13 and 15).

4. Discussion

We analyzed 1,900,920 HD-IIV3 and 223,793 aIIV3 recipients aged 65 years and older in senior members of large national managed care company in the U.S. Pooled over two seasons, HD-IIV3 was associated with lower hospitalization rates for respiratory as well as cardio-respiratory disease compared to aIIV3. More specifically, the adjusted rVE of HD-IIV3 versus aIIV3 for hospitalizations with underlying respiratory disease was 12% (95% CI: 3.3, 20%). The adjusted rVE of HD-IIV3 versus aIIV3 for hospitalizations with underlying cardio-respiratory disease was 7% (95% CI: 2.3, 12%).

Our findings are consistent with data from the U.S. Centers for Disease Control and Prevention. Indeed, Izurieta and colleagues reported that HD-IIV3 was associated with lower hospitalization rates for probable influenza (hospitalization with an administrative ICD-10 code of 489 on any position on the claim) when compared to aIIV3, with an rVE of 7.7%, (95% CI: 5.1%, 10.2%) in the 2017–18 season [18]. Similarly, we also estimated that HD-IIV3 was associated with reduced hospitalizations for respiratory disease. Of note, our outcome definition was different than Izurieta et al. in that it captured, in our primary analysis, all respiratory related hospital admissions during the influenza season. The specificity and sensitivity of our outcome and the one reported by Izurieta are therefore different. Further, Izurieta at al. used an inverse probability of treatment weighting (IPTW) method to balance differences between cohorts. However, propensity score methods adjust only for measured confounders, not unmeasured confounders. If HD-IIV3 recipients were frailer than aIIV3 recipients, residual confounding from unmeasured variables would bias the relative treatment effect to the null. For these two reasons, it is challenging to quantitatively compare the rVEs between our study and Izurieta et al; however, it is noteworthy that directionally HD-IIV3 is in both studies associated with reduced hospitalization rates compared to aIIV3.

Our study has multiple strengths. First, we used a method that adjusts for confounding from unmeasured variables through the use of the PERR method and measured variables through regression. The adjusted rate ratios in the baseline period (Table 3) suggest residual bias caused by unmeasured confounding factors [27]. Because of this observation, we feel it appropriate to use the PERR method. When comparing the effectiveness of IIV3-HD and IIV3-SD in the VHA population using the PERR method, Young-Xu and colleagues observed a similar pattern: the relative risk in the observa-

tion period was 1.16, suggesting IIV3-SD to be more effective than IIV3-HD [15]. The relative risk in the baseline period, however, was 1.54 suggesting a strong selection bias. Applying PERR resulted in a relative risk of 0.75 – more in line with a wide body of evidence consisting of both randomized and observational studies [10]. It might be helpful to keep in mind that PERR is in essence a form of difference-in-differences – a method widely used in the field of economics to adjust for unmeasured confounding factors [33].

Second, we included in our study a negative control outcome of UTI admissions where we expected no association between vaccination status and the outcome. Reassuringly we did not observe a treatment effect UTI in season 2017–18 and the pooled analysis. This allows us to assume that the PERR model was not misspecified. Third, by requiring an observation period of at least two weeks we created a minimal time window to observe outcomes. As a result, we excluded members with a high propensity of dying at time of vaccination, a confounding variable that is otherwise hard to measure [38], and members who received vaccination after June 16. Because we realize that any time subjects are excluded from an analysis, other biases might be introduced inadvertently, we dropped this requirement in a stability analysis. Last, we extensively tested the validity of our assumptions and design choices by including various stability analyses, which did not alter our findings in a clinically significant way (Supplemental Tables 7–15).

Our study also has limitations. First, the heterogeneity in influenza viral circulation and intensity from year to year limits the generalizability of the study results as the two seasons of our study where predominantly H3N2 with limited H1N1 or B circulation. In 2016–17, public health laboratories typed 76% of all positive influenza tests to be of H3N2, 2% were H1N1, and 22% were type B [39]. In 2017–18, the distribution was 60% H3N2, 11% H1N1, and 29% type B [2]. Additionally, because our study aIIV3 cohort in 2016–17 was over fivefold smaller than in 2017–18, our combined results were heavily influenced by the second season, in which a recent study demonstrated reduced protection from antibodies induced by vaccination to egg-propagated A/H3N2 compared with antibodies to the circulating a/H3N2 virus [40]. The impact on the current analysis, if any, is unclear because both HD-IIV3 and aIIV3 are egg-based vaccines. Of note, the 2016–17 season was characterized by a good match between circulating strains and vaccine antigens. The rVE for respiratory-related hospitalizations did not significantly decrease from season 2016–17 to season 2017–18. A possible explanation could be that egg-adaptation reduces overall vaccine effectiveness equally in both HD-IIV3 and in aIIV3. Second, although PERR is an adaptation of the well-established difference-in-differences method, it is unable to adjust for unobserved time-varying (from baseline to observation period) confounders. In addition, it assumes that outcome rate changes from baseline to observation period in the aIIV3 cohort are similar to those in the HD-IIV3 cohort, if they had received aIIV3 instead. This common ratio assumption is comparable with the parallel trend assumption of the difference-in-differences method [33]. Although this assumption cannot be tested, baseline and observation periods are relatively close together, which reduces the chance of violating this assumption for confounding factors like frailty, hospital/provider access issues and propensity to hospitalize. PERR cannot adjust for confounding factors that vary from baseline to observation period, like local influenza vaccination rates (impacting herd immunity), and local prevalence of influenza – if left unmeasured. In a stability analysis, we did measure these local confounding factors – the length of the peak influenza season and influenza vaccination rates in the general population – on the state level for season 2017–18 (Supplemental Table 4), the most geographically granular data available to us. When adding these confounding factors to the covariates of the primary analysis (Supplemental Table 10), we saw a slightly higher rVE for hospitalizations for respiratory disease in 2017–18: from 12% (95% CI: 2.1%, 21%) to 14% (95% CI: 3.4%, 24%). Matching on state resulted in even higher rVEs, but mainly driven by higher rate ratios in the baseline period, suggesting increased residual confounding (Supplemental Table 10). Our data did not allow for capturing of geographic heterogeneity of potentially time-varying confounding factors on a more granular level than the state level. Potential variation of weather, viral activity and vaccination rates within a state (e.g., at the county or postal code level) may confound our results. We could have further reduced confounding by indication had we excluded providers offering both vaccines at the same location at the same time. Although provider level details prevented us from excluding these providers, doing so might have come at the cost of increasing geographic heterogeneity of other confounding factors: when comparing HD-IIV3 with SD-IIV3, Izurieta and colleagues *matched* on provider to reduce this type of confounding [41].

Third, the size of the cohort in 2016–17 did not enable us to extract statistically significant inferences specific to that season. Notably, the rVE for respiratory-related hospitalization in that first season was 13% (95% CI: −6.4%, 32%) and the rVE against our negative control, where we estimated the rVE against UTI, was erratic and non-statistically significant.

As the use of the HD-IIV3 and aIIV3 grows, future effectiveness studies should attempt to examine more specific outcomes such as hospital admissions with a principal discharge code for pneumonia/influenza and hospital admissions following a positive influenza test. Our study was not able to study the former due to small cohort size and low incidence rates, and the latter due to absence of laboratory results data. However, these specific endpoints will take public health closer to understanding the causal link between these vaccines and preventing adverse health outcomes following an influenza infection.

5. Conclusion

Pooled over two predominantly A/H3N2 respiratory seasons, HD-IIV3 was associated with fewer respiratory- and cardio-respiratory-related hospital admissions than aIIV3 in senior members of large national managed care company in the U.S.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RVA and AC are employees of Sanofi Pasteur.

SG has received research support (investigator initiated grant funding) from Seqirus and Sanofi, consulting for Sanofi, consulting for Merck, speaker fees for Seqirus.

SMM has received research funding from Assurex, GSK, Merck, Pfizer, Roche and Sanofi, and is/was a member of advisory boards for GSK and Sanofi.

VM has received research funding from Sanofi-Pasteur, is Chair of the Independent Quality Committee at HCR Manor Care, and Chair of the Scientific Advisory Board and consultant at NaviHealth, Inc., as well as former Director of PointRight, Inc., where he holds less than 1% equity.

JW and MP declare that they have no known competing interests..

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.105.

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